SYNOPSIS

SYNTHESIS, BIOLOGICAL AND COMPUTATIONAL EVALUATION OF SOME NEW CHALCONES AND 1,5-BENZOTHIAZEPINES AS POTENTIAL ANTIMICROBIAL AND CYTOTOXIC AGENTS

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The thesis entitled **"SYNTHESIS, BIOLOGICAL AND COMPUTATIONAL EVALUATION OF SOME NEW CHALCONES AND 1,5-BENZOTHIAZEPINES AS POTENTIAL ANTIMICROBIAL AND CYTOTOXIC AGENTS"** describes the general methods of synthesis and characterization of some new chalcones and 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines. Since chalcones and benzothiazepines were widely reported to possess antimicrobial and cytotoxic activities, all the synthesized compounds were screened for these activities. The observed activities were also correlated with predicted activities carried out by computational studies. The thesis consists of 3 chapters and the content of each chapter is summarized below.

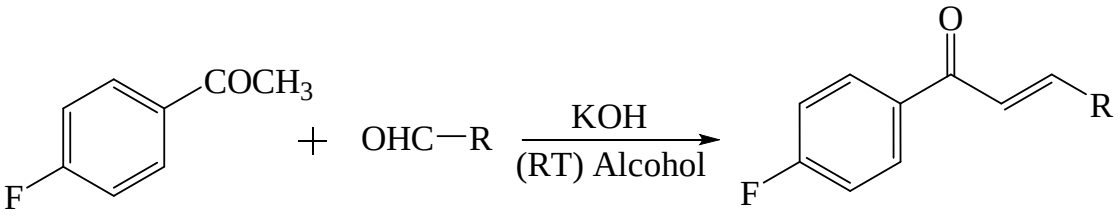
CHAPTER-1
SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NEW CHALCONES

A number of heterocyclic systems containing nitrogen can be successfully synthesized from 1,3, diaryl-propene-2ones, popularly called as chalcones, which in turn may be obtained by the Claisen-Schmidt condensation reaction between an aromatic/heteroaromatic methyl ketone and aromatic/heteroaromatic aldehydes in the presence of alkali. Chalcones are bichromophoric molecules separated by a keto-vinyl chain and constitute an important class of naturally occurring flavonoids exhibiting a wide spectrum of biological activities. The presence of a reactive, α,β-unsaturated keto functional group in chalcone is found to be responsible for their broad spectrum activity, which may be altered depending on the type and position of substituents on the aromatic rings.

This chapter provided an introduction to chalcones, literature survey on general methods of synthesis, spectral characteristics and biological importance of a number of chalcones. The chapter also described the synthesis, characterization and biological activities of some novel chalcones, prepared by the condensation between 4-fluoroacetophenone and various aromatic / heterocyclic aldehydes. The chalcones thus obtained were checked for their purity by T.L.C, then purified by crystallization and if necessary by column chromatography. The pure chalcones were then characterized by melting point, elemental analysis, I.R, NMR & mass spectral data. The chalcones so

obtained were subjected to antibacterial and antifungal activities by serial tube dilution method to determine the MIC values. The compounds were also subjected to cytotoxic activity based on MTT assay on different cell lines. The results were given in tables and then a discussion on the results was provided. Some of the chalcones found to possess significant antibacterial activity, particularly compounds with electron withdrawing substituents on the aromatic ring. The cytotoxic activity studies revealed the usefulness of some of these compounds on prostate cancer cell lines. At the end of the chapter references were provided.

General scheme of reaction



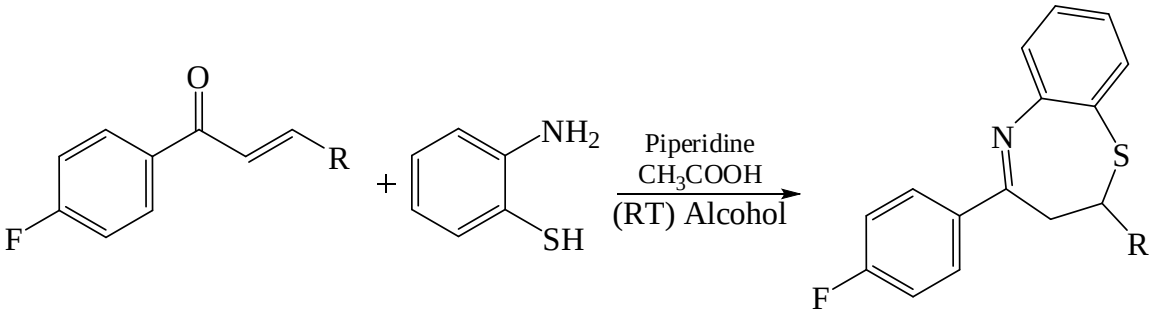
4-Fluoroacetophenone **Aromatic/ Heterocyclic aldehyde** **Chalcone derivative**

SCHEME-I

CHAPTER-2
SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NEW 1,5-BENZOTHIAZEPINES

An introduction to 1,5-benzothiazepines, their general methods of synthesis, spectral characteristics and therapeutic potential was provided in this chapter. The title compounds were obtained by the reaction between chalcones and guanidine hydrochloride. The resulting substituted 1,5-benzothiazepines were identified by TLC, purified either by crystallization or by column chromatography. The structures of the synthesized 1,5-benzothiazepines were established by elemental analysis, IR, NMR and mass spectral data. Since 1,5-benzothiazepines were reported to possess antimicrobial and cytotoxic activities, they were screened for these activities by following the procedures as described in chapter 1.

General scheme of reaction



Chalcone derivative **2-Aminothiophenol** **1,5-Benzothiazepine derivative**

SCHEME-II

A comparison of the antibacterial activities between chalcones and 1,5-benzothiazepines obtained from these chalcones clearly revealed that the chalcones were more potent than the benzothiazepines. This may be due to the presence of a reactive conjugated carbonyl system in chalcones which was missing in 1,5-benzothiazepines when chalcones were cyclized. It appears that the contribution from this conjugated system for antibacterial activity dominated the contribution from the 1,5-benzothiazepine structure, the other substituents being common in both the classes of compounds. A similar comparison of antifungal activities revealed a different picture as evidenced by the being chalcones more potent than the 1,5-benzothiazepines. In fact, such an observation can be justified by the fact that a number of research trails being employed in therapy as antifungals possess α,β-unsaturatedketone moiety in their structures.

A comparison of the cytotoxic activity between chalcones and benzothiazepines on the different cell lines tested, which clearly revealed the superiority of the benzothiazepines over chalcones. Many of the synthesized benzothiazepines exhibited significant cytotoxic activity as evidenced by IC_{50} values. However, some of the chalcones were also found to be cytotoxic in some cases particularly on prostate cancer cell lines. A list of references was provided at the end of this chapter.

CHAPTER-3

COMPUTATIONAL EVALUATION

The chalcones and the benzothiazepines synthesized were subjected to computational evaluation in order to have the correlation between the observed activities and predicted activities using atom based 3D-QSAR studies in the case of antibacterial and antifungal activities and Pharmacophore modeling in the case of cytotoxic activity. 3D-QSAR analysis was performed using Partial Least Square (PLS) method. The figures given in this chapter indicated unfavourable region for substitution (red region) and favourable region (blue region) for substitution for the compounds to exhibit antibacterial and antifungal activities. The observed – log MIC values from the actual results and the predicted – log MIC values from the PLS method were well correlated supporting the usefulness of these computational studies in predicting the antimicrobial activity in the case of chalcones and 1,5-benzothiazepines. The most potent and the least potent compounds could be identified from these studies and the results of these studies were consistent with the actual results.

A set of 25 chalcones and 20 benzothiazepines were subjected to Pharmacophore modeling using PHASE^{TM} software and further these pharmacophore models can be used as a reference to identify features required for the newly synthesized chalcones and benzothiazepines for their cytotoxicity. The generated pharmacophore models were used as potent virtual screening tools to identify potent chalcones and 1,5-benzothiazepines assumed to have well defined cytotoxic activity. The corresponding figures for chalcones and benzothiazepines were given. The studies could identify the most promising chalcones and benzothiazepines as cytotoxic agents and the responsible pharmacophoric features were identified.